REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-40 are pending after entry of the amendments set forth herein.

Claims 1-4, 6-15 and 30 were examined. Claims 1-4, 6-15 and 30 were rejected.

Claims 1, 2, 4, 9, 13 and 30 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Claims 38-40 are new. Support for the amendments to the claims is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 36 lines 15-20, page 70 line 17, figure 6B, where support for particular polynucleotide and polypeptide fragment lengths, and allelic variants may be found.

Accordingly, no new matter is added by these amendments.

Please replace claims 1, 2, 4, 9, 13 and 30 with the clean version provided above and add new claims 38-40.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Priority

The Office has noted that the application appears to claim subject matter disclosed in a prior copending application which is not incorporated into the first paragraph of the application. The Office has further noted that there are some inconsistencies between the first paragraph of the application and the declaration.

Enclosed herewith, Applicants have filed an Applicant Data Sheet (ADS) including the correct priority information. Applicants have also amended the first paragraph of the application to reflect the correct priority information.

Applicants wish to point out that the submission of an ADS should be sufficient to assert priority. As stated in the M.P.E.P. 601.05, with respect to an ADS, "(5) *Domestic priority information*. This

information includes the application number, the filing date, the status (including patent number if available), and relationship of each application for which a benefit is claimed under 35 U.S.C. 119(e), 120, 121, or 365(c). Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and § 1.78(a)(2) or § 1.78(a)(4), and need not otherwise be made part of the specification." (emphasis added).

Applicants wish to thank the Office for noting the inconsistencies and respectfully submit that the inconsistencies have been addressed by the ADS and amendment.

Sequence Compliance

The Office has stated that the application fails to comply with the requirements of 37 CFR 1.821-825 because it contains a sequence, KIAA0716, that is not accompanied with the relevant sequence identifier.

KIAA0716 is represented by SEQ ID NOS:24, 31 and 43 which are referenced in the paragraph beginning on page 6, line 20. This paragraph been amended to reference KIAA0716 in such a way that that KIAA0716 is accompanied by these sequence identifiers.

This objection is believed to have been addressed by this amendment, and the Applicants respectfully submit that the application complies with the requirements of 37 CFR 1.821-825.

Objections to the specification

The Office Action stated that the status of applications referenced throughout the disclosure should be updated. No applications are issued, and, as such, the status of the applications have not been updated.

The Office Action states that the Applicants are required to delete embedded hyperlinks. The paragraph beginning on page 12, line 32, has been amended to recite the "world wide website of the National Center for Biotechnology Information".

The Office Action states that a new title is required, and a title is suggested. The Applicants have amended the title to a title that is similar to the suggested title.

Applicants respectfully submit that these objections have been addressed and the objections to the specification may be withdrawn.

Claim objections

The Office Action states that Claim 1 is objected to because it is assertedly missing the term "least".

Applicants respectfully submit that this objection has been addressed in the amended claims, and the objection may be withdrawn.

Statement of Availability

With respect to Claim 3, which recites material deposited at the ATCC, a Statement of Availability is enclosed stating that the clones are deposited and publicly available. Also, a receipt from the ATCC for the deposit of the claims is enclosed.

Applicants submit that the rejection of Claim 3 under 35 USC 112, first paragraph have been addressed by this Statement, and the rejection may be withdrawn.

Claim Rejections under 35 USC 101 and 112, first paragraph- utility/enablement

Claims 1-4, 6-15 and 30 are rejected under 35 USC 101, assertedly because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Claims 1-4, 6-15 and 30 are further rejected under 35 USC 112, first paragraph assertedly because one of skill in the art would not know how to use the claimed invention if it lacks utility. Since both rejections are established using the same reasons, Applicants respectfully traverse these rejections together, as they are applied to the revised claims.

Any rejection based on lack of utility should include a detailed explanation as to why the claimed invention has no specific and substantial credible utility[1] and whenever possible, the Office should provide documentary evidence[1]. In the absence of documentary evidence, the Office should provide a *prima facie* showing that establishes that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the Applicants for the claimed invention. A *prima facie* showing must contain the following elements: (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record[1]. A rejection based on lack of utility should not be maintained if an

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[1] *Fed. Reg. Vol. 66 at page 1098, Section II-B, paragraph 3.*

asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.[2]

In making this rejection, the Examiner states that various functions for CLASP-3 in various immune responses are discussed in the application, and appears to assert that because the specification provides no experimental evidence that CLASP-3 is involved in an immune response, the utility is not substantial.

Applicants wish to point out that in view of the teachings of the present specification, several utilities for CLASP-3 would be apparent to one of skill in the art.

As will be explained below, one of skill in the art would recognize that CLASP-3, based on its significant homology to CLASP-1, as taught by Applicants, and b) its expression pattern in immune cell lines, is involved in an immune response. As such, one of skill in the art would recognize several utilities for CLASP-3 nucleic acids, including, for example, detecting a cell of the immune system, or modulating an immune response.

The Guidelines for Examination of Applications for Compliance with the Utility Requirement (Federal Register Vol 66 No. 4, Jan 5, 2001), "The Utility Guidelines", to which Examiners must follow in determining utility, states that an assertion of utility based on homology may be sufficient to establish that a nucleic acid has a specific, substantial and credible utility. No *pro se* ruling has been established, and each determination of utility should be fact based.

The Utility Guidelines state "when a patent application claiming a nucleic acid asserts a specific, substantial and credible utility, and bases the assertion upon homology to existing nucleic acids or protein having an accepted utility, **the asserted utility must be accepted by the examiner** unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion" (emphasis added). The Utility Guidelines, quoting Fujikawa v. Wattanasin[3] further notes that "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient."

Figure 4A and Figure 8 of the instant patent application shows a sequence alignment of CLASP-3 with other members of the CLASP family including CLASP-1. As can been seen from these sequence

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[2] *Utility Examination Guidelines, Federal Register (Jan. 5, 2001) Vol. 66(4):1092-1099, emphasis added.*
3 Fujikawa v. Wattanasin, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996)

alignments and discussion in the specification, all CLASP molecules have a similar structure in that they have cadherin EC motifs, putative transmembrane domains, a number of putative ITAM domains and a high degree of sequence identity. Figure 8 of the instant application also shows CLASP family sequence alignments, and shows boxes of high similarity between all CLASP family members. As such, CLASP-3 is similar, both in terms of structure and sequence to CLASP-1.

CLASP-1 is the subject of patent application 09/546,934, presently in allowance. As shown in the 09/546,934 patent application, CLASP-1 is a molecule that plays a critical role in cell-cell communication, and is thought to be part of a developmental "switch" that initiates a developmental pathway in response to certain cell-cell interactions. For CLASP-1, these cell-cell interactions occur during immune responses and typically involve B- and T-cells interactions. CLASP-1 has also been shown to involved in production of interleukin-2 during T-helper cell responses, and, as such, has a variety of utilities. Applicants respectfully submit that CLASP-3, because it shares a high degree of sequence identity with CLASP-1, also plays a critical role in cell-cell communication, and, as such, has similar utilities to that of CLASP-1. Applicants submit that this assertion is supported by the expression patterns of the CLASP gene family members. For example, CLASP-1, 4 and 5 are differentially expressed in B and T cells in the human immune system, indicating that all six CLASP proteins have a similar function. CLASP-3, although it has a different tissue expression profile than CLASP-1, 4 and 5 (see Fig. 2A and Table 2 of the instant application), is expressed in B- and T- cell lines (see Fig. 2B). The expression pattern of CLASP-3 in B- and T-cell lines supports the idea that CLASP-3 functions in the same way as CLASP-1.

Applicants acknowledge that the reports of Skolnick, Bork, Doerks, and Smith, as cited in the Office Action, indicate that that sequence similarity alone, particularly when performed by software robots, or in the context of database annotation, may be insufficient to identify the biological role of a polypeptide. However, the role of sequence similarity in determining genetic function cannot be ignored. For example, see the attached publication by Enright et al., which states "In particular, it is well known that members of the same protein family may possess similar or identical biochemical functions. Protein families can be defined as those groups of molecules which share significant sequence similarity. . . . Well characterised proteins within a family can hence allow one to reliably assign functions to family members whose functions are not known or not well understood." The Guidelines state that "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient" (emphasis added). A reasonable correlation is provided by the present

application.

In view of the specific utility of the claimed sequences, Applicants respectfully request that the rejection of claims 1-4, 6-15 and 30 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 USC 112, first paragraph- enablement

Claims 1-4, 6-11, 14-15 and 30 are rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Office Action asserts that the claims are not enabled because the specification fails to provide enablement for polynucleotides that hybridize to SEQ ID NO:1 under stringent conditions, variants of SEQ ID NO:1, and nucleic acids with 95% sequence identity to SEQ ID NO:1. In making the rejection, the Office Action states that "the specification does not teach any allelic variants". Applicant traverse this rejection as it is applied to the revised claims.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[4]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[5]

For the sake of brevity, Applicants will refer to the genus of nucleic acids encompassed by the claims as SEQ ID NO:1 and "variants" of SEQ ID NO:1. Applicants respectfully submit that they have

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4 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

5 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

provided several working examples of variants, and also provided a significant amount of guidance as to how variants that retain biological activity may be made.

Applicants have provided several examples of variants in their working examples

In Figure 6B of the application, several polymorphisms (i.e. allelic variations) in the CLASP-3 sequence are described. These polymorphisms lead to 6 single nucleotide variants and one alternative splice variants. As such, the instant application explicitly discloses the sequence at least 7 CLASP-3 variants. These variants are to different types: single nucleotide polymorphisms and splice variants.

Figure 6B states that the 7 polymorphisms may be present singly or in any combination in the CLASP-3 sequence, leading to a large number of permutation of polymorphisms. The actual number of permutations of these polymorphisms is 7! (7-factorial), or over 5040. As such, figure 6B describes over 5040 possible variants of CLASP-3. Applicants respectfully submit that one of skill in the art would recognize that a large number of CLASP-3 allelic variants are described in the working examples.

As such, contrary to the statements made in the Office Action, several (at least 13 and up to about 5000) allelic variants are described in the working examples of the instant application. Applicants respectfully submit that the number of variants described in the working examples alone, are sufficient for enabling the CLASP-3 variants of the claims.

Applicants have provided extensive guidance as to how to make variants that retain biological activity

The Office Action states that no guidance is provided to allow a skilled person to modify CLASP-3 and retain its biological activity. The question to which the Office Action seems most concerned is: does the specification teach a skilled artisan to change the sequence of CLASP-3 while maintaining the CLASP-3 activity, without resorting to undue experimentation?

Throughout the instant specification, for example on page 40, line 25 to page 41, line 11, and page 68, line 1 to page 69 line 32, the Applicants have provided several methods for modifying CLASP-3. One of skill in the art would recognize that the answer to the above question, i.e., which amino acids can be replaced while maintaining activity, is taught by Applicants.

The specification provides, for example in Figure 8, a sequence alignment of all of the known CLASP molecules. Upon viewing this figure, one of skill in the art would recognize that the amino acids that are conserved (i.e. the amino acids marked with an asterisk "*") have greater importance for CLASP function than other amino acids. Similarly, a skilled person would recognize that CLASP-3

amino acids that are conservatively substituted (i.e. marked with a colon ":") could be predictably interchanged with amino acids of the same type (the types described on page 67 of the specification). Because the substitution merely substitutes one amino acid with a similar amino acid that is present at an identical position in a very similar protein, it would be recognized that this substitution could be made without abolishing activity of the CLASP-3 protein. One of skill in the art would recognize that there is even greater flexibility for amino acid substitutions in non-conserved amino acids in the CLASP-3 sequence.

In a similar manner, Figure 8 shows that the CLASP-3 sequence contains motifs known as "ITAM" motifs that are known to contain Ile/Leu variation at the fourth position of the motif (see e.g., Borroto et al, Biopolymers. 1997;42(1):75-88; abstract enclosed herewith). A skilled person, upon seeing these motifs in view of Borroto's ITAM variants, would make these substitutions with a predictable lack of effect on ITAM motif function, and hence the activity of the CLASP protein would not be affected.

Also, the Examiner should note that the have provided several polymorphisms for other CLASP molecules (e.g. CLASP-4, in application number 09/736,969 and CLASP-5, in application number 09/736,960, etc.). Since the various members of the CLASP family are very similar to each other, one of skill in the art would recognize that the polymorphism for other CLASPS e.g. those of CLASP-4 and CLASP-5, may be used as guidance for producing further variants of CLASP-3.

As such, the specification provides a substantial amount of guidance as to which amino acids of the CLASP-3 sequence may be changed without abolishing CLASP-3 activity. The Applicants respectfully submit that one of skill in the art would be able to modify the sequence of CLASP-3 while maintaining CLASP-3 activity without resorting to undue experimentation.

In summary, the Applicants respectfully submit that the specification provides a large number of working examples of variants, and has provided significant guidance as to which CLASP-3 amino acids could be changed to maintain CLASP-3 activity. Applicants respectfully request withdrawal of this rejection.

If the Office chooses to rebut Applicants arguments, the Office is reminded that extensive experimentation may be performed, so long as the experimentation is routine, and that every species within a genus does not have to be operative for a claim to be fully enabled.[6]

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[6] *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). *Hybritech v. Monoclonal*

Claim Rejections under 35 USC 112, first paragraph- written description

Claims 1-4, 6-11, 14-15 and 30 are rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventors (s), at the time the application was filed, has possession of the claimed invention. Specifically, the Office Action asserts that the specification fails to provide description of polynucleotides that hybridize to SEQ ID NO:1 under stringent conditions, variants of SEQ ID NO:1, and nucleic acids with 95% sequence identity to SEQ ID NO:1. Applicants traverse this rejection as it is applied to the revised claims.

The standard for written description has been established over several years of court cases such as *Vas-Cath Inc. v. Mahurkar*[7] and *In re Wertheim*[8] and has culminated in the publication of the "Written Description Guidelines" Federal Register Vol. 66 No. 4, dated January 5, 2001 to which the Office must adhere to when making a written description determination. The law of written description does not requires that the specification specifically describe all species that are encompassed by the claims.

A landmark and often cited case involving written description of nucleic acid invention is *Regents of the University of California v. Eli Lilly & Co*[9], hereafter "Lilly". Lilly states that:

> "A description of a genus of cDNAs may be achieved by means of a recitation of **a representative number of cDNAs**, defined by nucleotide sequence, falling within the scope of the genus **or** of a recitation of **structural features** common to the members of the genus."

As such, according to the Law, the written description requirement for a genus of nucleic acids may be satisfied by a) a representative number of species, **or** b) a recitation of structural features common to all members of the species.

As established above, the specification describes a large number of CLASP-3 species in Figure 6B. Applicants respectfully submit that this number of CLASP-3 species represents a representative number of nucleic acid species to describe the genus of nucleic acid species recited in the claims. As

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Antibodies, Inc. 231 USPQ 81 (Fed. Cir. 1986)
7 *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).
8 *In re Wertheim* 191 U.S.P.Q. 90 (C.C.P.A. 1996)
9 *Regents of the University of California v. Eli Lilly & Co* 119 F.3d 1559 (Fed. Cir. 1997) at 1568-69

such, the Applicants submit that the specification has met the written description requirement for the instant claims.

Applicants respectfully submit that the foregoing discussion overcomes the rejections.

To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

The Applicants further submit that by providing a full length CLASP-3 nucleic acid and polypeptide sequences, the specification provides a structural feature common to all members of the genus. Support for this assertion may be found in the "Synopsis of Application of Written Description Guidelines" (hereafter "the Synopsis"; posted on the USPTO world wide website on March 1, 2000).

With regard to “hybridization” claims, Applicants respectfully submit that Fig. 6B of the instant application shows the results hybridization experiments using a portion of SEQ ID NO:1. As such, Applicants respectfully submit that they have described several species that are encompassed by the subject claims that recite hybridization at high stringency as a limitation, e.g. new claim 39.

Example 9 of the Synopsis describes a similar fact pattern involving a hypothetical nucleic acid and unsequenced nucleic acids that hybridize under conditions of high stringency to the hypothetical nucleic acid. Example 9 of the Synopsis discusses “hybridization”-type claims, i.e. claims like the subject claims that recite a nucleic acid that specifically hybridizes to an exemplary sequence. With respect to analysis of hybridization-type claims, the Synopsis states “a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.” As such, the Synopsis clearly states that stringent hybridization conditions, like those of the instant claims, yield nucleic acids that are adequately described. As such, according to the Synopsis of the Application of Written Description Guidelines, nucleic acid molecules that hybridize to SEQ ID NO:1 should be adequately described by the sequence of SEQ ID NO:1. These conclusion drawn in the analysis of Example 9 is reiterated in Example 10 of the Synopsis, which discusses “product by process”- type claims, where the product is a nucleic acid obtained by the process of hybridization.

Based on the foregoing, the Applicants respectfully submit that the specification provides a) representative number of species *and* b) a recitation of structural features common to all members of the species to satisfy the written description requirement.

Applicants respectfully assert that the rejection of Claims 1-4, 6-11, 14-15 and 30 are rejected under 35 U.S.C. § 112, first paragraph, as being not adequately described in the specification has been adequately addressed. In view of the foregoing arguments, withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 USC 103a

Claims 1, 6-11, 14-15 and 30 are rejected under 35 USC 103(a) as unpatentable over Hillier (Genbank Accession number AA429436), in view of Sibson (WO 94/01548). The Office Action asserts that Hillier discloses an isolated polynucleotide that, in view of Sibson's vectors, host cells and methods of producing peptides, renders the claims obvious. The Applicants respectfully traverse this rejection as it applied to the revised claims.

The claims are directed to polynucleotides that a) encode at least 200 contiguous amino acids of SEQ ID NO:2, or b) have at least 600 contiguous nucleotides of SEQ ID NO:1.

Hillier's polynucleotide exhibits sequence identity to the CLASP-3 nucleotide sequence over about 588 contiguous nucleotides, and encodes a polypeptide exhibits identity to the CLASP-3 polypeptide sequence over about 196 amino acids. Hillier's polynucleotide does not encode a polypeptide that has at least 200 contiguous amino acids of identity with the CLASP-3 polypeptide, and does not have a region of at least 600 contiguous nucleotides that is identical to the CLASP-3 nucleotide sequence.

As such, Hillier is deficient in that it fails to teach at least one element of each of the claims.

Sibson's vectors, host cells and methods of producing peptides fail to meet this deficiency, and, as such, Hillier and Sibson, either alone or in combination, fail to teach at least one element of the claimed invention.

Accordingly, Claims 1, 6-11, 14-15 and 30 are not made obvious by Hillier in view of Sibson under 35 U.S.C § 103 and these rejections may be withdrawn.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number VITA-003.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 02-14-2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The title is changed as follows:

~~CLASP-3 TRANSMEMBRANE PROTEIN~~

--NUCLEIC ACID MOLECULE ENCODING A CLASP-3 MEMBRANE PROTEIN--

The paragraph beginning on page 1, line 3 is amended as follows:

--This application claims priority to U.S. Application Ser. Nos. 60/240,508, 60/240,503, 60/240,539, 60/240,543, **09/687,837** (all filed Oct. 13, 2000); 09/547,276, 60/196,267, 60/196,527, 60/196,528, 60/196,460 (all filed Apr. 11, 2000); 60/182,296 (filed Feb. 14, 2000), 60/176,195 (filed Jan. 14, 2000), 60/170,453 (filed Dec. 13, 1999), 60/162,498 (filed Oct. 29, 1999), 60/160,860 (filed Oct. 21, 1999).--

The paragraph beginning on page 6, line 20, is amended as follows:

--Figure 3. A. Amino acid sequence of human and rat CLASP proteins. Sequences were aligned using ClustalW. One letter amino acid abbreviation used. Protein motifs are found within the labeled boxes. "-" indicates gaps that are placed to acquire a best overall alignment. Other abbreviations: "HC2A" Human CLASP-2 sequence (SEQ ID NO:9), "KIAA" KIAA1058 sequence (SEQ ID NO:10) (Genbank Accession No. AB028981), "rat" TRG gene (SEQ ID NO11) (Genbank Accession No. X68101), "HC4" Human CLASP-3 sequence (SEQ ID NO:12), "HC1" Human CLASP-1 sequence (SEQ ID NO:13), "HC3" Human CLASP-3 sequence (SEQ ID NO:14), "HC5" Human CLASP-3 sequence (SEQ ID NO:15). B. Alignment of DOCK motifs found within the human CLASPs **and KIAA0716** (SEQ ID NOS:16-20, 24, 25, 27-43, 47 and 49-55) and compared to canonical DOCK motifs (SEQ ID NO:21-23, 32-34, 44-46 and 56-58). Consensus amino acids found within all DOCK motifs are also indicated.--

The paragraph beginning on page 12, line 32, is amended as follows:

--Another preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., 1977, Nuc. Acids Res. 25:3389-3402 and Altschul et al., 1990, J. Mol. Biol. 215:403-410, respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the **world wide website of the** National Center for Biotechnology Information ~~**(http://www.ncbi.nlm.nih.gov/)**~~. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always>0) and N (penalty score for mismatching residues; always<0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, 1989, Proc. Natl. Acad. Sci. U.S.A. 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.--

IN THE CLAIMS

Claims 1, 2, 4,9, 13 and 30 are amended as follows:

1. **(twice amended)** An isolated Cadherin-like asymmetry protein-3 (CLASP-3) polynucleotide, wherein said polynucleotide **encodes at least 200 contiguous amino acids of SEQ ID NO:2 or a biologically active variant thereof** ~~**is**~~

~~**(a) a polynucleotide; a polynucleotide that has the sequence of SEQ ID NO: 1 or**~~

~~(b) a polynucleotide that hybridizes under stringent hybridization conditions comprising wash conditions of 0.2X SSC and 0.1% SDS at 45oC to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue of a polypeptide having the sequence of SEQ ID NO: 2; or~~

~~(c) a polynucleotide that hybridizes under stringent hybridization conditions comprising wash conditions of 0.2X SSC and 0.1% SDS at 45oC to (a) and encodes a polypeptide with at 25 contiguous residues of the polypeptide of SEQ ID NO: 2; or~~

~~(d) a polynucleotide that hybridizes under stringent hybridization 11 conditions comprising wash conditions of 0.2X SSC and 0.1% SDS at 45°C to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1.~~

2. **(amended)** The polynucleotide of claim 1**, wherein said polynucleotide encodes at least 200 contiguous amino acids of SEQ ID NO:2 or an allelic variant thereof.** ~~that encodes a polypeptide having the full-length sequence of SEQ ID NO:2.~~

4. **(amended)** An isolated ~~cadherin-like asymetry protein 3 (~~CLASP-3~~)~~ polynucleotide comprising a nucleotide sequence that has at least 90% percent identity to SEQ ID NO:1 **or an allelic variant thereof**.

9. **(amended)** A host cell comprising the polynucleotide of claim 1, wherein the nucleotide sequence of the polynucleotide is ~~operatively~~ **operably** linked with a regulatory sequence that controls expression of the polynucleotide in a host cell, or progeny of the cell.

13. **(amended)** An isolated ~~DNA that encodes a Cadherin-like asymetry protein-3 (~~CLASP-3~~)~~ **polynucleotide comprising at least 600 contiguous nucleotides of SEQ ID NO:1 or allelic variant thereof.** ~~protein as shown in SEQ ID NO:2.~~

30. **(amended)** A ~~pharmaceutical~~ composition comprising a polynucleotide of claim 1 and a ~~pharmaceutically acceptable~~ carrier.